contains 8 potency units in accordance with the U.S. standard typhoid vaccine.

2. *Labeling*—a. *Recommended use/indications.* Routine immunization is not recommended in the United States. Selective immunization is, however, indicated in the following situations: (1) Intimate exposure to a known typhoid carrier as would occur with continued household contact; (2) community or institutional outbreaks of typhoid fever; and (3) foreign travel to areas where typhoid fever is endemic.

Primary immunization; dosage and schedule: (a) Adults and children over 10 years of age; 0.5 mL subcutaneously on two occasions, separated by 4 or more weeks; and (b) children 6 months to 10 years of age; 0.25 mL subcutaneously on two occasions, separated by 4 or more weeks.

Booster doses should be given at least every 3 years under conditions of continued or repeated exposure to typhoid as follows: Adults and children over 10 years of age, 0.5 mL subcutaneously or 0.1 mL intradermally; and children 6 months to 10 years of age, 0.25 mL subcutaneously or 0.1 mL intradermally.

b. *Contraindications.* Immunization of persons with acute febrile illness or other active infection should be deferred.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No information from studies conducted on this particular product.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No controlled studies are presented. Over the past 10 years, several million doses of the vaccine have been distributed in Texas without reports of serious reactions.

c. *Benefit/risk ratio.* Assuming the product is effective, the benefit-to-risk assessment should be satisfactory. (See Generic Statement.)

4. *Critique.* The vaccine is killed and preserved by heat and phenol. In addition, thimerosal is added as a preservative. The latter should not affect the vaccine adversely although field trials have not yet confirmed this assumption. However, such field trials with this vaccine are not feasible in the foreseeable future.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Typhoid Vaccine (Acetone Inactivated) Manufactured by Wyeth Laboratories, Inc.

1. *Description.* This typhoid vaccine contains 1 billion acetone killed *Salmonella typhi* (Ty 2 organisms) per mL. The organisms are inactivated by precipitation with acetone and warming at 37 °C for 24 hours. The vaccine is distributed in dried form with a sterile diluent containing 0.5 percent phenol as a preservative for reconstitution.

2. *Labeling*—a. *Recommended use/indications.* For primary immunization for adults and children of 10 years of age and older, 2 doses of 0.5 mL each, injected subcutaneously or intramuscularly, are recommended with an interval of 4 or more weeks. For children 6 months through 9 years of age, the subcutaneous or intramuscular injection of 2 doses of 0.25 mL each is recommended at an interval of 4 or more weeks. For reinforcement of immunity for adults and children of 10 years of age and older, 0.5 mL injected subcutaneously or intramuscularly is recommended. For children 6 months through 9 years of age, the dose for reinforcement is 0.25 mL, injected subcutaneously or intramuscularly. The timing of reinforcement doses is not specified, but instead reference is made to military recommendations, inasmuch as this product is used primarily by the Armed Forces. Intradermal innoculation is contraindicated.

b. *Contraindications.* The manufacturer recommends deferral of immunization in the presence of an acute respiratory or other active infection.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Field trials conducted by the World Health Organization employing vaccines very similar to this product have displayed a high degree of efficacy.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Typhoid vaccines in general produce high rates of local reactions and some systemic reactions, neither of which are serious. Severe reactions are very rare. This preparation appears to yield reactions at rates no greater than those expected.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this vaccine is satisfactory when compared with typhoid vaccines in general. (See Generic Statement.)

4. *Critique.* This is one of the few available typhoid vaccines which has been prepared by methods virtually identical to those vaccines which were most efficacious in field trials. Its efficacy is therefore well established.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Typhoid Vaccine (Heat-Phenol Inactivated) Manufactured by Wyeth Laboratories, Inc.

1. *Description.* The typhoid vaccine contains 1 billion *Salmonella typhi* (Ty 2 strain) heat-phenol killed organisms per mL. The organisms are killed by suspending them in sodium chloride, heating to 56 °C for 1 hour, and then adding 0.5 percent phenol and maintaining the batch at room temperature thereafter for 4 days. Phenol 0.5 percent is added as a preservative in the final diluent.

2. *Labeling*—a. *Recommended use/indications.* For primary active immunization of adults and children greater than 10 years of age, 2 doses of 0.5 mL each subcutaneously are recommended at an interval of 4 or more weeks. For children of 6 months to 10 years of age, 2 subcutaneous doses of 0.25 mL are recommended with an interval of 4 or more weeks. When necessary to comlete immunization in a shorter period of time, the manufacturer recommends the above doses administered subcutaneously on three occasions at weekly intervals.

If necessary to maintain immunity, the manufacturer recommends a reinforcing dose at least every 3 years. However, if an interval of more than 3 years has elapsed since the last dose, a single reinforcing dose is satisfactory. Reinforcing doses for adults and children over 10 years of age comprise either 0.5 mL subcutaneously or 0.1 mL intracutaneously. For children 6 months to 10 years of age, 0.25 mL subcutaneously or 0.1 mL intracutaneously is recommended.

b. *Contraindications.* The manufacturer recommends deferral of immunization in the presence of an acute respiratory or other active infection.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Field trials conducted by the World Health Organization employing vaccines very similar to this product have displayed efficacy.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Typhoid vaccines in general produce high rates of local reactions and some systemic reactions,

neither of which are serious. Severe reactions are very rare. This preparation appears to yield reactions at rates no greater than those expected.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this vaccine is satisfactory when compared with typhoid vaccines in general. (See Generic Statement.)

4. *Critique.* This heat phenol inactivated typhoid vaccine is analogous to those found effective by field trials (see Table I) and would therefore appear to be efficacious.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Reference

(1) BER VOLUME 2050.

Passive Immunization Products

Generic Statement on Botulinus Antitoxin

Botulism is a paralytic disease caused by the action of a protein neurotoxin elaborated by *Clostridium botulinum. Clostridium botulinum,* a spore-forming organism closely related to *Clostridium tetani,* is widely distributed in nature and can regularly be found in soils and from marine sources. Six types of *Clostridium botulinum* (A–F) are recognized; each produces an immunologically distinct neurotoxin. These are among the most powerful toxins known; 1 microgram contains 200,000 minimal lethal doses for a mouse, and is very close to the lethal dose for man.

The disease usually results from the ingestion of uncooked food of animal origin, e.g., sausage, spiced meat, or smoked fish, or improperly canned fruits or vegetables, in which spores of the organism contaminated the product, germinated, and produced toxin. Food that is not obviously spoiled may still contain botulinus toxin. Thus, the disease is usually not an infection, but rather an intoxication. However, occasional cases of botulism result from infection of a surgical or traumatic wound with *Clostridium botulinum,* followed by toxin production in vivo. There is also strong suggestion that some cases of botulism result from toxin formation by *Clostridium botulinum* organisms in the human gastrointestinal tract.

Most human botulism is caused by types A, B, and E. Botulism caused by improperly canned vegetables or improperly preserved meat products is generally due to types A or B; most of the type E botulism reported in the United States has been traced to fish or fish products. Only two outbreaks of type F botulism have been reported. Types C and D produce disease almost exclusively in animals.

Although the spores are relatively heat resistant, requiring pressure sterilization to ensure killing, botulinus toxin is relatively heat-labile, being completely inactivated by a temperature of 100 °C for 10 minutes.

The disease is rare, but often fatal. From 1910 to 1919, 246 cases were reported in the United States. A series of studies by K.F. Meyer and his associates in the early 1920's defined the epidemiology of botulism, the foods most often incriminated, and the conditions necessary for the destruction of *Clostridium botulinum* spores. These studies led to strict controls on the commercial canning industry, and most cases of botulism in the last 25 years have followed consumption of improperly canned, home-preserved foods. From 1970 to 1973, 30 outbreaks of foodborne botulism, involving 91 cases and 21 deaths, were reported to the Center for Disease Control. Six cases of wound botulism were reported during the same period. Very recently, investigators in California have described a syndrome of infant botulism; the epidemiology and pathogenesis of botulism in children less than 1 year of age is currently under active investigation.

Treatment of botulism is directed toward three major goals. First, unadsorbed toxin should be removed from the gastrointestinal tract. This can be accomplished by an emetic if the suspected food was recently ingested, or more commonly by purging and enemas. Second, circulating neurotoxin can be neutralized by the administration of antitoxin. It is unlikely that antitoxin has any neutralizing effect on toxin already fixed to nerve tissue. Finally, assisted respiration is used to compensate for the neuromuscular blockade and to tide the patient over the period of respiratory paralysis.

Nature of Product

Botulism antitoxin trivalent, types A, B, and E, and botulism antitoxin, type E, consist of the partially purified globulin fraction from the serum of horses hyperimmunized with multiple sequential doses of botulism toxoid.

Production

Botulism antitoxin, types A, B, and E, are generally produced in the same animal by immunizing horses with subcutaneous injections of alum-precipitated formalinized toxoids prepared from *Clostridium botulinum,* types A, B, and E. To produce monovalent type E botulism antitoxin, only the type E toxoid is used for immunization. Hyperimmunization is begun with subcutaneous injections of gradually increasing amounts of the liquid toxoid at weekly intervals. Trial bleedings are taken periodically, and when antitoxin titers are sufficiently high, the serum is harvested by plasmapheresis. The plasma is pooled, defibrinated, subjected to pepsin digestion, followed by ammonium sulfate fractionation, dialyzed, and adjusted to yield approximately a 20-percent concentration of serum proteins. An average of 50 percent of the antitoxin activity originally present in the plasma is recovered in the final concentrate.

The digested, fractionated, dialyzed product is adjusted to a concentration suitable for filling, and tested for identity, safety, and potency in units per mL in toxin-antitoxin neutralization tests in graded dilutions in groups of mice. Phenol is added as a preservative to a concentration of 0.45 percent w/v, and the product is filled with a 20 percent excess or more, according to Federal standards related to the stated expiration date.

Recommended use/indications

Evidence concerning the exact amount of circulating antitoxin needed to neutralize experimental botulinus toxin poisoning is incomplete. Animal evidence suggests that the outcome of treatment depends largely on the time interval elapsing after the onset of symptoms, and before the peak of circulating administered antitoxin is reached. Therefore, it is strongly recommended that patients should be treated promptly with botulism antitoxin trivalent types A, B, and E, as soon as the clinical diagnosis of botulism is suspected. Prior to the injection of this material, if circumstances permit, the patient should be questioned regarding any history suggesting sensitivity to horses or horse serum, and should be tested for such sensitivity by conjunctival (1:10 dilution) or intradermal (1:100 dilution) tests with the serum for freedom from reactions. Suitable test kits for this purpose are sometimes available. Some experts advocate instead a tolerance test with 0.1 mL of a 1:100 dilution given subcutaneously. No test system is totally reliable, and the patient must be watched for at least 1 hour after the antitoxin has been injected.

Best results in the treatment of botulism are likely to be obtained if large doses of antitoxin are given early

in the disease, the object being to provide an excess of circulating antitoxin as early as possible. In order to ensure the most rapid neutralization of all toxin in the tissue and fluids, most authorities recommend prompt intravenous administration of one vial (7,500 International Units of type A, 5,500 International Units of type B, and 8,500 International Units of type E) injected very slowly at a dilution of 1:10, the solution to be at ambient temperature before being injected.

In order to provide a reservoir of antitoxin for subsequent adsorption, an additional equal dose may be given by intramuscular injection. Further doses are indicated in 2 to 4 hours if the signs and symptoms worsen. Because antitoxin remains in the circulation for over 30 days, the recommended dose should be given immediately, rather than in multiple small doses administered over a long period.

The recommended prophylactic dose for an individual who has eaten food suspected of being infected with *Clostridium botulinum* is 1,500 to 7,500 International Units of type A, 1,100 to 5,500 International Units of type B, and 1,600 to 8,500 International Units of type E given intramuscularly, depending on the amount of food eaten. If signs or symptoms of botulism appear, further treatment should be initiated with intravenous antitoxin.

Unless there is unequivocal evidence that the disease under treatment or preventive therapy is type E botulism, the trivalent antitoxin (types A, B, and E) is always recommended. If the disease is known to be type E botulism, therapy with monovalent type E antitoxin is justified. Individuals who exhibit apparent sensitivity to horse serum should nevertheless receive antitoxin, employing recommended schedules for gradual desensitization with increasing doses of antitoxin administered over several hours until the total dose has been given.

Safety

Federal regulations specify that botulism antitoxin be tested to ensure sterility and contain an appropriate preservative in specified amounts. The product must meet prescribed test results for freedom from pyrogenicity in animals.

The most significant problems regarding the safety of botulism antitoxin relate to sensitivity to horse serum. Two types of hypersensitivity reactions occur: anaphylaxis and serum sickness. These reactions cannot always be predicted in advance by sensitivity testing, and may not be prevented by desensitization.

Anaphylactic reactions to horse serum, fortunately the less common of the two, can occur without any known prior sensitization. They occur immediately or within a few minutes following injection, and are manifest by severe respiratory distress, collapse, and shock. Even with prompt administration of epinephrine, death may occur in 10 percent or more of cases.

Serum sickness following horse serum occurs 6 to 21 days after an individual's first injection. Prior sensitization is not required, although previous injections increase the likelihood of serum sickness and decrease the latent period between injection and onset of symptoms to as little as a few hours. The larger the dose of serum, the more likely is serum sickness to occur. Rates of serum sickness following horse serum vary, but range from 2 to 30 percent, and are directly dose dependent. In the most recent U.S. experience, however, only 7 percent of recipients of botulism antitoxin developed serum sickness. The overall rate of adverse reactions reported to the Center for Disease Control was 21 percent.

Efficacy

There is limited evidence that type E antitoxin is effective in preventing death in man when given after the onset of symptons, but there is little data on the efficacy of types A and B in man. In animals, type E and type A antitoxins appear to be effective, but the efficacy of type B antitoxin has never been conclusively demonstrated.

Almost all of the human botulism outbreaks in Japan have been due to type E. In 20 outbreaks before antitoxin was used, mortality rate was 28 percent; in 15 outbreaks after the use of type E antitoxin began, the mortality rate was reduced to 4 percent. The two groups may not have been comparable in other respects such as quality of supportive therapy or the duration of symptoms prior to treatment. In the more recent reports of type E botulism in the United States, as reported by Koenig and Whittaker, five of seven patient not given type E antitoxin died, but none of eight patients given type E antitoxin died. Again, the treated and untreated patients may not have been comparable in other respects. There is thus evidence, albeit uncontrolled, of the effectiveness of botulism antitoxin in man but only for type E.

Despite the lack of convincing evidence as to the efficacy of types A and B botulism antitoxin, the advisability of its use is firmly established in medical practice, and will presumably continue so unless chemical means are devised to circumvent the neuroparalytic effects of botulinus toxin.

Special Problems

Botulism is fortunately a rare disease in the United States. The number of cases reported in the past 10 years has varied annually from a low of 5 to a high of 34.

Since one consequence of rising food prices may well be an increase in home canning, education of the home canner and consumer is the most pressing need in the prevention and control of botulism. Public health agencies should provide information to the home canner about proper techniques and common errors involved in the preservation of foods.

The recent increase in contaminated commercial products suggest that new Federal regulations for canning low-acid foods are crucial to the prevention of processing errors by the canning industry. This should be a joint responsibility of the Center for Disease Control, the Food and Drug Administration, and the Department of Agriculture. Control measures developed and initiated by the smoked fish industry after three outbreaks involving smoked fish in the mid-1960's serve as a model for responsible action by the food industry.

Botulinus toxoid is available to permit development of botulism immune globulin of human origin. With so few cases occurring every year, this has understandably been given a rather low priority in research and development of biological products.

Serveral reports have appeared since 1967 describing the use of guanidine hydrochloride in the treatment of botulism. The drug is thought to act by enhancing the release of acetylcholine from nerve terminals. Reported cases have generally shown improvement with oral doses of 35 to 50 mg per kg per day, and in some instances the beneficial effect of the drug has been documented with neurophysiologic studies. Nevertheless, these studies have not been controlled, and the efficacy of guanidine hydrochloride and other drugs that act at the myoneural junction remains in question. For these reasons the use of these drugs should not preempt the administration of botulism antitoxin.

Recommendations

(1) Encourage educational programs directed at the home canner; (2) encourage the enforcement of Federal regulations established for the canning of low-acid foods and other high risk foods in the commercial industry; (3)

give consideration to the development of botulism immune globulin of human origin; and (4) support studies designed to elucidate the mechanism of action of botulinus toxin and the developemnt of pharmacologic agents that circumvent or minimize the neuroparalytic effects of the toxin.

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SPECIFIC PRODUCT REVIEWS

Botulism Antitoxin, types, A, B, and E and Botulism Antitoxin, Type E Manufactured by Connaught Laboratories Limited

1. *Description.* Botulism antitoxin, types A, B, and E, and monovalent type E, as supplied by Connaught Laboratories, is a refined and concentrated preparation of globulins modified by enzymatic digestion. The product is obtained from horses immunized with botulism toxoids, types A, B, and E, or type E alone. The product is purified and concentrated by ammonium salfate precipitation, pepsin digestion, and ultrafiltration. Phenol is added as a preservative at a concentration of 0.45 percent w/v.

Extensive details of the manufacturing process are provided. The trivalent product contains 7,500 International Units of type A antitoxin, 5,500 International Units of type B antitoxin, and 8,500 International Units of type E antitoxin per vial (10 mL). The monovalent product contains 5,000 International Units of type E antitoxin per 2 mL vial.

2. *Labeling*—a. *Recommended use/indications.* The product is recommended for the prevention and/or treatment of botulism.

b. *Contraindications.* There are extensive precautionary statements about testing for sensitivity to horse serum, but no absolute contraindications are specified.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* **This product meets Federal requirements. A toxin-antitoxin neutralization test is carried out in mice** for each individual component of the trivalent antiserum to determine the unitage.

(2) *Human.* No specific data are cited, but frequent references are made to the work of Dolman, in Vancouver, A statement is made in the submission (Ref. 1), as follows:

> To date our botulism antitoxin is used in Canada and is stocked by the National Communicable Disease Center, Atlanta, Georgia. From their reports in Morbidity and Mortality we can assume that when the antitoxin is administered the effect is lifesaving in most cases.

Such an assumption is unjustified. However, the report of the Tennessee epidemic (see Generic Review), not cited in the manufacturer's submission, demonstrated the efficacy of type E antitoxin.

b. *Safety—(1) Animal.* This product meets Federal requirements.

(2) *Human.* According to the Center for Disease Control's surveillance of reactions to botulism antitoxin, a 17-percent frequency of reactions to this product is mentioned in the Morbidity and Mortality Weekly Report.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The labeling is clear and adequate.

5. *Recommendations.* The Panel recommends that these products be placed in Category I and that the appropriate license(s) be continued.

Botulism Antitoxin Manufactured by Lederle Laboratories Division, American Cyanamid Co.

No data have been provided by the manufacturer for botulism antitoxin for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendation. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

Reference

(1) BER VOLUME 2061.

GENERIC STATEMENT

Diphtheria Antitoxin

Diphtheria is an infectious and communicable disease of man which usually involves the upper respiratory tract and sometimes produces skin infections. The causative agent is *Corynebacterium diphtheria*, a gram-positive bacillus with metachromatic granules. Upper respiratory diphtheria is characteristically associated with the production of a pseudomembrane in the nasal passage, pharynx, and/or larynx, and with the appearance of systemic symptoms due to absorption of an exotoxin. Fifty years ago there were approximately 200 cases per 100,000 population in the United States each year (roughly 200,000 cases annually). This has decreased to a rate of about 0.1 per 100,000 population in recent years (200 to 400 cases annually). Approximately 10 percent of patients with diphtheria succumb. Death may be due to respiratory obstruction by the membrane or to remote effects of the toxin upon the myocardium or peripheral nervous system.

Because the morbidity and mortality of diphtheria are largely a consequence of the toxin elaborated by the organism, antiserum (antitoxin) prepared by immunizing horses has been used by nearly 80 years in the treatment of the disease and for its prevention in exposed, susceptible individuals. This approach to control of the disease is only partially successful, because the disease is already well established by the time it is recognized, and toxin that has been absorbed and fixed to cells is unaffected by antitoxin.

Further, antitoxin does nothing to prevent spread of the toxigenic causative organism. Penicillin or other effective antibiotic agents will usually eradicate the organism but, because they have no effect against toxin, **antibiotics are only an adjunct to therapy of clinical diphtheria.**

Since neither passive immunization with antitoxin nor therapy with antimicrobial agents provides an entirely satisfactory approach to the control of diphtheria, active immunization of humans against the toxin is the safest, most effective control measure. The reduction in morbidity and mortality from diphtheria in the United States during the past half century is largely attributable to widespread immunization against the toxin. But

because significant segments of the U.S. population have not received adequate active immunization against diphtheria employing the toxoid, between 200 and 400 cases of diphtheria continue to occur yearly. For these individuals therapy with antitoxin is required.

Description

Diphtheria antitoxin is a preparation of hyperimmune serum prepared in horses immunized against diphtheria toxin.

Production

Diphtheria antitoxin is prepared by hyperimmunizing horses with diphtheria toxoid and diphtheria toxin until high levels of serum antitoxin activity are achieved. The horses must be demonstrated to be free of communicable disease.

Plasma containing satisfactory titers of antitoxin is concentrated by precipitation and dialysis and usually partially refined by pepsin digestion. Final concentration of antitoxin is at least 500 units per mL. Sterilization is achieved by microfiltration and an appropriate preservative is added. Each lot must meet requirements for sterility and freedom from pyrogenicity according to Federal regulations. Potency is tested by comparison with U.S. standard antitoxin.

Use and Contraindications

The major use of diphtheria antitoxin is for the treatment of clinical diphtheria. Treatment should be initiated immediately, prior to definitive bacteriologic diagnosis, in individuals in whom there is reasonable clinical suspicion of diphtheria. Delay in administration is to be avoided, because the antitoxin only neutralizes circulating toxin; toxin already fixed to tissue is unaffected. Delay allows increasing amounts of toxin to bind to tissue and is associated with a progressive increase in case fatality.

The dose of antitoxin recommended by most authorities is between 20,000 and 80,000 units, depending on the size of the patient, the severity, and duration of infection. The entire dose should be given at one time; some authorities recommended that up to one-half be given intravenously and the rest intramuscularly. Because sensitivity to horse serum is frequent in humans, sensitivity testing and a carefully taken history of any findings suggesting sensitivity to horses, horse dander, or horse serum are mandatory. Tests should be performed by both intradermal and conjunctival routes, with extreme precautions in case of any adverse reactions. Individuals with diphtheria exhibiting apparent sensitivity to horse serum nevertheless should receive antitoxin, employing recommended schedules for gradual "desensitization" with increasing doses of antitoxin administered over several hours until the total dose has been given.

Important adjuncts to therapy include general supportive measures, maintenance of the airway in patients with laryngeal diphtheria (diphtheritic croup), and administration of antimicrobial drugs active against *Corynebacterium diphtheriae* (erythromycin, lincomycin, penicillin, rifampin). Antimicrobial drugs, however, are only adjuncts to therapy and must not be used instead of antitoxin.

For the prevention of diphtheria in exposed, susceptible individuals (persons who are Schick test positive and/or who have not been immunized), diphtheria antitoxin, 1,000 to 5,000 units administered intramuscularly, may be used subsequent to testing for sensitivity to horse serum (see Special Problems).

There are no absolute contraindications to the use of diphtheria antitoxin in the presence of diphtheria.

Safety

Federal regulations specify that diphtheria antitoxin must be tested to ensure sterility and contain an appropriate preservative in specified amount. The product must meet prescribed tests for freedom from pyrogenicity.

The most significant problems regarding the safety of diphtheria antitoxin relate to sensitivity to horse serum. Two types of hypersensitivity reactions occur: anaphylaxis and serum sickness. These reactions cannot always be predicted in advance by sensitivity testing, and may not be prevented by densensitization.

Anaphylactic reactions to horse serum, fortunately the less common of the two, can occur without any known prior sensitization of any identifiable sort. They occur immediately or within a few minutes following injections and most characteristically comprise collapse and shock. Even with prompt administration of epinephrine, death may occur in 10 percent or more cases.

Serum sickness following horse serum occurs 6 to 21 days after an individual's first injection. Prior sensitization is not required, although previous injections increase the likelihood of serum sickness and decrease the latent period between injection and onset of symptoms to as little as a few hours. The larger the dose of serum, the more likely is serum sickness to occur. The major manifestations of serum sickness are fever, arthritis, lymphadenopathy and urticaria. Fatalities are rare except in instances of laryngeal edema. Symptoms persist for days or weeks. Rates of serum sickness following horse serum vary and are directly dependent on the dose. Indeed, the administration of 100 mL produces serum sickness in 90 percent of recipients.

Efficacy

The degree of effectiveness of diphtheria antitoxin in the therapy of diphtheria is not precisely established. Although many studies are reported, most are beset with problems of study design sufficient to cause concern about the exactitude of the results. For example, a number of studies indicate that individuals who received antitoxin in the first day or two of the illness exhibited fewer complications and increased survival compared to those receiving treatment later, but there are questions about the comparability of cases treated early and late. However, in the early experience, when supplies of antitoxin were erratic, the contrast between patients treated with it and those unable to be so treated was reported as very striking. Further, there appear to be secular changes in the severity and incidence of diphtheria, negating comparisons from year-to-year and decade-to-decade.

Nonetheless, most authorities believe that diphtheria antitoxin does exhibit salutary effects on the course, complications, and mortality of the disease, and that such effects are more pronounced the earlier in the course the antitoxin is given. However, it is clear that at best antitoxin fails to reduce mortality below about 5 percent.

Even less clear is the degree of effectiveness of antitoxin in the prevention of diphtheria in exposed, susceptible individuals. The administration of an antimicrobial drug in therapeutic doses to exposed, susceptible individuals avoids the use of horse serum and although not proven in controlled clinical trials, should be an effective alternative regimen. Erythromycin appears to be the most effective; penicillin, lincomycin, or rifampin are nearly as effective.

Special Problems

Diphtheria antitoxin as used for the production of passive immunity in the treatment or prevention of diphtheria exhibits two special problems.

1. Diphtheria antitoxin is only partially effective in treatment, apparently because it neutralizes only circulating toxin. Toxin that has already